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26. (Twice Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean $t_{1/2}$ from 2.8 to 4.4.

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27. (Amended) The method of claim 1, further comprising administering to said human patients at least one additional pharmaceutically active ingredient for treatment of NIDDM.

28. (Amended) The method of claim 1, further comprising administering to said human patients an additional pharmaceutically active ingredient for treatment of NIDDM, said additional pharmaceutically active ingredient selected from the group consisting of a sulfonylurea, a glitazone or a second biguanide.

29. (Amended) The method of claim 1, in which the dose of metformin comprises metformin hydrochloride.

REMARKS

Reconsideration of the present application is respectfully requested. An early and favorable action on the merits is earnestly solicited.

I. Status of the Claims

Claims 1, 4-5, 7-15, and 18-31 are pending; claims 2-3, 6, 16-17, and 32-34 have been cancelled without prejudice; and claims 1, 4-5, 7-15, and 19-29 have been amended without prejudice. It is respectfully submitted that no new matter has been added by virtue of this amendment.

II. Rejection of Claims 1-31 under 35 U.S.C. §112, first paragraph

In the Office Action, claims 1-31 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that "[t]he instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation." The Examiner directs the Applicants attention to *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) and the eight factors discussed therein when assessing if a disclosure would have required undue experimentation.

The Examiner notes that "these examples are neither exhaustive, nor define the class of compound required," and that "[t]he pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity." The Examiner further states that "the instant claims read on all antihyperglycemic drug compositions where the maximum plasma concentration occurs from 5.5-7.5 hours after administration, necessitating an exhaustive search for the embodiments suitable to practice the claimed invention."

In response and in order to advance the prosecution of the present application, claim 1 has been amended without prejudice to recite "metformin" in place of "antihyperglycemic drug." The claims of the present application are clearly enabled for metformin or a pharmaceutically acceptable salt thereof, and as amended, the present claims do not "read on all antihyperglycemic compositions".

In any event, Applicants are not required to exemplify every formulation which would be encompassed by the claim and it would be tremendously costly, inefficient and perhaps unethical to require manufacturing and testing of alternative formulations as apparently deemed necessary by the Examiner in the last Office Action. At the time the present application was filed, there were numerous controlled release technologies in the art, and testing for drug-plasma levels is routine in clinical studies.

Therefore, it is respectfully submitted that once the T_{max} range which provides for a useful dosage form has been established, other controlled release technologies known in the art can be manipulated and tested to achieve this T_{max} range without undue experimentation as discussed below.

A. The Test for Enablement

It is well recognized that "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 8 USPQ2d at 1046 (1989). "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *In re Wands*, 8 USPQ2d at 1404 (*citations omitted*). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id. (Emphasis added)*. The very nature of pharmaceuticals requires both formulation work and clinical (in-vivo) evaluation, and therefore giving due regard for the nature of the invention, the amount of experimentation needed to prepare a suitable controlled release formulation using a technology other than that exemplified in the specification does not amount to undue experimentation.

B. Dosage Forms and Plasma Profile of the Present Invention

In the Office Action the Examiner states that "Applicant fails to set forth the criteria that defines the dosage form or steps in the production of the composition that results in the dosage form having the instant claimed plasma profile," and that "Applicant fails to provide information allowing the skilled artisan to ascertain the plasma profile without undue experimentation."

The invention as claimed is directed to a method of treatment wherein a maximum plasma concentration is obtained at 5.5 to 7.5 hours after administration, irrespective of the particular technology employed in the controlled release dosage form. Certain representative examples of these formulations are provided in the present application, and it is explained have stated in the specification that a number of controlled release technologies are useful in order to obtain the claimed pharmacokinetic parameters of the present invention.

Examples 1-3 of the present application which are directed to a tablet formulation containing metformin HCl, a seal coating, and a sustained release coating. Example 3 of the present application described clinical studies which were conducted to evaluate formulations prepared in accordance with Examples 1-3, which together with the specification enable the claimed methods of lowering blood glucose levels in human patients with oral controlled release dosage forms of metformin or a pharmaceutically salt thereof which provide the T_{max} values of the present invention. The Examiner's attention is respectfully directed to page 19, line 21 to page 20, line 14 which states the following:

> Other controlled release technologies known to those skilled in the art can be used in order to achieve the controlled release formulations of the present invention, i.e., formulations which provide a mean T_{max} of the drug and/or other pharmacokinetic parameters described herein when orally administered to human patients. Such formulations can be manufactured as a controlled oral formulation in a suitable tablet or multiparticulate formulation known to those skilled in the art . . . .

In addition, at the time the application was filed, numerous controlled release technologies were well within the knowledge of pharmaceutical formulators having ordinary skill in the art. Such pharmaceutical formulators know that controlled release technologies can be manipulated, e.g., by varying the amount of controlled release carrier (among other things), to provide a formulation which upon in-vivo testing will provide the T_{max} range of the present invention. This fact is supported, e.g., by a simple review of patents discussed in the specification concerning formulation technologies, which patents provide ranges of ingredients. These ranges represent the acknowledgement of those skilled in the art that a certain amount of experimentation is considered to be necessary to manipulate a controlled release technology to

obtain a desired release pattern of the drug. Such release patterns are demonstrated by the (well-known) use of in-vitro dissolution testing, which is considered by pharmaceutical formulators of ordinary skill in the art to provide guidance as to which particular formulations might provide the desired in-vivo performance.

Next, it is well known to those of ordinary skill in the art that upon formulating prospective products which might be useful in humans, in-vivo clinical studies must be conducted to determine whether the prospective product actually provides the desired in-vivo performance. Plasma profiles are routinely obtained during clinical trials and in particular during phase I-III studies as indicated in J.T. Cartensen, Pharmaceutical Principles of Solid Dosage Forms, 1993 (attached herewith).

It is respectfully submitted that none of the above steps, either separately or collectively, rise to the level of undue experimentation. Once the goal has been identified and has been attained (as in the present exemplified formulations set forth in the specification), it is respectfully submitted that a pharmaceutical formulator of ordinary skill in the art can manufacture prospective dosage forms for evaluation (to determine if they meet the required in-vivo parameters), a clinician of ordinary skill in the art can administer the dosage forms and draw blood at appropriate time intervals, and a pharmacokineticist of ordinary skill in the art can evaluate the in-vivo blood plasma results.

These steps represent a clear pattern followed by every pharmaceutical company in the world. There is no alternative short-cut known which is considered to be acceptable by government regulatory agencies (such as FDA). Since human experiments with pharmaceuticals are generally considered unethical if being done solely for patent purposes, the Examiner appears to be requiring this Applicant to conduct studies that are unethical, unnecessary and not legally required to support the rightful scope of Applicant's claims. Accordingly, it is earnestly requested that the Examiner remove this basis for rejection.

The Examiner is reminded that Applicants are not required to exemplify every formulation which would be encompassed by the claim. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 84 (CCPA 1970); MPEP 2164.01(b) (8th Edition) ("As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied.").

In *Telectronics*, for example, the court found that "[s]ince one embodiment is admittedly disclosed in the specification, along with the general manner in which its current range was ascertained, we are convinced that other permutations of the invention could be practiced by those skilled in the art without undue experimentation." *Telectronics,* 8 USPQ2d at 1223 (*citing SRI Int'l v. Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1121, 227 USPQ 577, 586 (Fed. Cir. 1985) (the law does not require an applicant to describe in his specification every conceivable embodiment of the invention)).

Therefore, it is respectfully submitted that by virtue of the present application Applicants have disclosed a T_{max} range which provides for a useful dosage form of metformin or a pharmaceutically acceptable salt thereof, and other controlled release technologies known in the art can be manipulated by one of ordinary skill in the art to achieve this T_{max} range without undue experimentation.

C. U.S. Patent No. 6,099,859

In the rejection, the Examiner states that "[i]n the instant case, the provided examples set forth dosage forms made according to a process where the dosage forms have the same composition as those of U.S. 6,099,859 ('859)." However, the Examiner notes that " '859 discloses that the peak plasma profile is approximately 8-12 hours after administration, whereas the instant specification/claims state that the dosage forms, which appear to have the same composition and process of making as '859, have a peak plasma profile of 5.5-7.5 hours."

(1) The specification of '859 states in a preferred embodiment, that peak plasma levels are obtained between 8-12 hours after administration (See column 2, lines 50-55).

(2) In actuality however, the exemplified formulations did not provide a T_{max} between 8-12 hours except when the formulation prepared in accordance with Example 3 was administered at dinner. As set forth in an Information Disclosure Statement which will subsequently be hand delivered to the Examiner, the mean T_{max} values for the Examples of the '859 were as follows: Example 1 (fasting) 4.67 hours; Example 2 (fasting) 4.33 hours; Example 2 (fed a.m.) 6.80 hours; Example 3 (fed a.m.) 6.67 hours; Example 3 (Fed p.m.) 9.67 hours. Therefore, the only instance the T_{max} was between 8-12 hours was Example 3 fed in the P.M. (at dinner).

The claims have now been amended to state the "T_{max} of metformin at from 5.5 to 7.5 hours after single dose administration following dinner." The claims as now written are directed to methods and treatments which were never accomplished in the Examples of the '859 patent.

With respect to the Examiner's position that the provided examples of the present application set forth dosage forms made according to a process where the dosage forms have the same composition as those of U.S. 6,099,859 ('859), the Examiner's attention is respectfully directed to the fact that the formulations exemplified and tested in the present application are indeed different as the formulations of the Examples of the present application differ from those of the '859 by having two laser drilled holes, and the method achieved a different result than that reported in the '859 or achieved by clinical testing of Examples 1-3. However, it is respectfully submitted that one skilled in the art would be able to manipulate the processes and formulations of the '859 by other methods to obtain the claimed pharmacokinetic parameters of the present invention by routine experimentation.

Therefore, in view of the aforementioned, it is respectfully submitted that the formulations of the present invention are different than those of the '859 patent.

D. Conclusion

In the specification, Applicants have provided formulations, methods of making the formulations, and clinical studies of these formulations, that support the limitations (e.g., T_{max} values) recited in the present claims. Further, the prior art is replete with controlled release technology and, as stated in the present application, a number of controlled release technologies can be used to manufacture formulations which provide the results recited in the present claims without undue experimentation. Therefore, the Examiner is respectfully requested to remove the 35 U.S.C. §112 rejection of the pending claims.

III. Rejection of Claims 22-25 under 35 U.S.C. 112, second paragraph

Claims 22-25 were rejected under 35 U.S.C. 112, second paragraph, on the grounds of indefiniteness.

Specifically, the Examiner states that "[r]ecitation of 'based on' in claims 22-25 is indefinite since it is unclear whether Applicant is claiming that the dose of administration for metformin is 'X' mg after an evening meal or whether another dose of metformin provides these limitations. In the event the $AUC_{0\text{-infinity}}$ for a particular dose of metformin is claimed, amendment with 'for administration' is suggested to overcome the instant rejection."

In response and for purposes of advancing the prosecution of the present application, claims 22-25 have been amended without prejudice to recite the term "for" administration rather than "based on" administration, as suggested by the Examiner.

In view of the actions taken, the Examiner is respectfully requested to remove the rejection of claims 22-25 under 33 U.S.C. 112, second paragraph.

IV. Rejection of Claims 32-34 under 35 U.S.C. 102(b) as being anticipated by Cheng et al (WO 99/47125).

Claims 32-34 were rejected under 35 U.S.C. 102(b) "as being anticipated by Cheng et al (WO 99/47125; hereafter '125)". The Examiner states that "'125 discloses controlled release antihyperglycemic dosage form that has the same composition taught by the specification as providing the instant mean fluctuation indexes."

In view of the present amendment, claims 32-34 of the present application have been canceled without prejudice rendering the Examiner's rejection moot. Therefore, the Examiner is respectfully requested to withdraw the rejection of claims 32-34 under 35 U.S.C. §102(b) for the above-referenced application.

V. Conclusion

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

It is now believed that the above-referenced rejections and objections have been obviated and it is respectfully requested that the rejections and objections be withdrawn. It is believed that all claims are now in condition for allowance.

According to currently recommended Patent Office policy the Examiner is requested to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

An early and favorable action is earnestly solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claims 2-3, 6, 16-17, and 32-34 have been cancelled without prejudice.

The claims have been amended as follows:

1. (Twice Amended) A method for lowering blood glucose levels in human patients needing treatment for non-insulin-dependent diabetes mellitus (NIDDM), comprising orally administering to human patients on a once-a-day basis at least one oral controlled release dosage form comprising an effective dose of **[at least one suitable antihyperglycemic agent] metformin** or a pharmaceutically acceptable salt thereof and **an effective amount of** a controlled release carrier **to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form**, wherein **following oral administration of a single dose,** the dosage form provides a mean time to maximum plasma concentration (T_{max}) of **[agent] metformin** at from 5.5 to 7.5 hours after administration **following dinner**.

4. (Amended) The method of claim **[3] 1**, in which the administration of the at least one metformin dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7.0 hours after administration.

5. (Amended) The method of claim **[3] 1**, in which the administration of the at least one metformin dosage form occurs at dinner time and provides a mean time to maximum plasma concentration (T_{max}) of metformin at from **[about]** 5.5 to 7.0 hours after the administration.

7. (Amended) The method of claim **[3] 1**, in which the administration of the at least one metformin dosage form provides a width at 50% of the height of a mean plasma

concentration/time curve of **[the drug]** **metformin** from about 4.5 to about 13 hours.

8. (Amended) The method of claim **[3]** 1, in which the administration of the at least one metformin dosage form provides a width at 50% of the height of a mean plasma concentration/time curve of **[the drug]** **metformin** from about 5.5 to about 10 hours.

9.(Amended) The method of claim **[3]** 1, in which the administration of the at least one metformin dosage form provides a mean maximum plasma concentration (C_{max}) of metformin which is more than about 7 times the mean plasma level of said metformin at about 24 hours after administration.

10. (Amended) The method of claim **[3]** 1, in which the administration of the at least one metformin dosage form provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 7 times to about 14 times the plasma level of said metformin at about 24 hours after administration.

11. (Amended) The method of claim **[3]** 1, in which the administration of the at least one metformin dosage form provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 8 times to about 12 times the plasma level of said metformin at about 24 hours after administration.

12. (Amended) The method of claim **[3]** 1, in which the administration of the at least one metformin dosage form provides a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, **for** **[based on]** administration of a 2000 mg once-a day dose of metformin.

13. (Amended) The method of claim **[3]** 1, in which the administration of the at least one metformin dosage form provides a mean maximum plasma concentration (C_{max}) of metformin from about 1700 ng/ml to about 2000 ng/ml, **for** **[based on]** administration of a 2000 mg once-

a-day dose of metformin.

14. (Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ from at least 80% of the mean $AUC_{0\text{-}24}$ provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

15. (Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ that is from at least 90% of the mean $AUC_{0\text{-}24}$ provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

19. (Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 33900 ng.hr/ml, **for [based on]** administration of a 2000 mg once-a-day dose of metformin.

20. (Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 26500 ng.hr/ml, **for [based on]** administration of a 2000 mg once-a-day dose of metformin.

21. (Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ from about19800 ng.hr/ml to about 33900 ng.hr/ml, **for [based on]** administration of a 2000 mg once-a-day dose of metformin.

22. (Twice Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml, **for [based on]** administration of a 1700 mg once-a-day dose of metformin

[after an evening meal].

23. (Twice Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0-\infty}$ of 20335 ± 4360 ng·hr/ml and a mean C_{max} of from 2053 ± 447 ng/ml, **for** **[based on]** administration of a 2000 mg once-a-day dose of metformin **[after an evening meal]**.

24. (Twice Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24} of 26818 ± 7052 ng·hr/ml and a mean C_{max} of 2849 ± 797 ng/ml, **for** **[based on]** administration of a 2000 mg once-a-day dose of metformin **[after an evening meal]**.

25. (Twice Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24} of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14th day of administration, **for** **[based on]** administration of a 2000 mg once-a-day dose of metformin **[after an evening meal]**.

26. (Twice Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean **[$T_{1/2}$]** $t_{1/2}$ from 2.8 to 4.4.

27. (Amended) The method of claim **[3]** **1**, further comprising administering to said human patients at least one additional pharmaceutically active ingredient for treatment of NIDDM.

28. (Amended) The method of claim **[3]** **1**, further comprising administering to said human patients an additional pharmaceutically active ingredient for treatment of NIDDM, said additional pharmaceutically active ingredient selected from the group consisting of a sulfonylurea, a glitazone or a second biguanide.

29. (Amended) The method of claim **[3]** **1**, in which the dose of metformin comprises metformin hydrochloride.